Comments of
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Regarding Listing by NTP of Alcoholic Beverages as Carcinogens

My comments will address only the association between alcohol drinking and cancer of the oral cavity, pharynx, larynx, and esophagus. Dr. Rubin will address the association between alcohol drinking and cancer of the breast and liver. It appears, also, that the designation by the NTP of alcoholic beverages as a known carcinogen is based almost entirely on the NTP's assessment of epidemiological associations at these six sites.

As in many recent publications, the Draft RoC Background Document for Alcoholic Beverage Consumption starts by referring to the 1988 IARC Monograph on Alcohol Drinking as unassailable proof that alcohol drinking causes cancer of the oral cavity, pharynx, larynx, esophagus and liver. I was an official observer for the preparation of that Monograph and noted that the final opinion was not unanimous among the members of the working group.

Some of the salient data for the dissent among the members of the working group were published in a letter to the editor (British Journal of Cancer 66, 1200-1201, 1992) by several colleagues and me. A copy of that letter to the editor has already been supplied to the NTP. It was never rebutted satisfactorily by the staff at IARC.

In summary, firstly, at the time of the preparation of that Monograph, there were no adequate studies demonstrating cancer in experimental animals from administration of alcohol. Consequently, the evaluation was based solely on epidemiological studies. Secondly, virtually all the epidemiological studies were confounded by cigarette smoking. And lastly, those few studies not obviously confounded failed to show an increase or in some cases actually showed a decrease in the incidence of cancer. These three observations continue to be problems with all the publications that have appeared since that Monograph.

The NTP Background Document acknowledges the continued lack of supportive animal studies and also acknowledges the problem of confounding by tobacco smoking in cohort studies; consequently, the Document cites the largest case-control studies and the Longnecker and Tseng review as evidence for the classification.

SLIDE 1

This slide quotes Longnecker's review, which appears to be the position of the Document, "the effect of alcohol among lifelong nonsmokers has been clearly demonstrated"; however, the three references do not support that statement. The paper by Ng et al. actually contradicts the Longnecker statement. Not only were the nonsmokers not lifelong nonsmokers, but Ng and colleagues found no association with wine and liquor and concluded that the association may

have little to do with alcohol and that contaminants of beer may be important etiologic factors. The use of this reference by Longnecker is simply misinformation.

SLIDE 2

The other two references (Blot et al. and Baron et al.) have serious flaws to prevent the conclusion of a "clearly demonstrated" effect of alcohol among lifelong nonsmokers. There was either no effect, or it was unknown, in drinkers of less than four or five drinks per day. Above this level of consumption other risk factors, such as oral hygiene and diet may be significant.

SLIDE 3

The risk estimates in the case-control studies on cancer of the oral cavity and pharynx are stated to all have been adjusted for smoking. Adjustment is problematic at best; it does not always fit the shape of the actual dose-response curve and can obscure a zero or even negative effect in nonsmokers. However, some of the case-control studies cited in the Document do contain the raw data on nonsmoking drinkers. Those data contradict the findings from adjustments. This slide shows that several reports found either no increase or an actual decrease, particularly at lower levels of consumption.

In France and Italy there are so few nondrinkers that the effect at lower levels of consumption cannot be ascertained. Control ("nondrinker") groups in studies in France and Italy were those consuming 40 grams of pure alcohol (Brugere et al., 1986) or 5 drinks (Franceschi et al ,1990) per day because there were so few actual nondrinkers. This, of course, will not only obscure a "J" shaped curve (protective at low doses), but if a "J" shaped curve exists, this combining of groups at low doses will make any effect at higher doses appear greater.

SLIDE 4

This slide shows the same analysis for laryngeal cancer. Even with adjustment some reports fail to show a dose-response. The Wynder papers certainly do not support an effect in nonsmokers.

SLIDE 5

This slide shows the same analysis for esophageal cancer. Even with adjustment, two studies fail to show an increase below levels of consumption which may be those of an alcoholic. At these levels other risk factors such as diet, oral hygiene, etc. confound the results. The paper by Tuyns in 1983 is not included in the Document, but it contains raw data on one of the largest groups of nonsmokers with esophageal cancer. The data are presented also for drinkers at lower levels of consumption; this is unusual in France. There is a "J" shaped curve for both males and females which Tuyns did not recognize because he combined drinkers under 40 grams per day as "nondrinkers". If one instead combines the data for males and females to increase the group sizes, the same "J" shaped curve remains with greater confidence. Furthermore, Tuyns' use of the 0-40 gram/day group (who had odds ratios less than unity) as the reference group makes the

odds ratios for other levels of alcohol consumption higher than they would be if the true nondrinkers had been the reference group. This "J" shape curve has been reported by others for alcohol and cancer.

SLIDE 6

This is a graph of the Tuyns data in nonsmoking men and women for levels of consumption up to 120 gms/day; the group consuming more than 120 gms/day had an even higher odds ratio and is not shown. Is one to say that alcohol is an anticarcinogen below 60 grams of alcohol per day? One might also take the position that above 100 grams it may be carcinogenic or that other risk factors become important. In any event, in my opinion, it is a simplistic, unscientific interpretation of the data to merely label the substance as "known carcinogen". Many, if not most people, for personal reasons, will be much more interested in the consumption level below 60 grams per day.

SLIDE 7

Finally, a comment on the mechanisms of carcinogenesis proposed in the document. Acetaldehyde was listed by IARC as an animal carcinogen solely from studies when it was administered by chronic inhalation at doses that caused necrosis of the respiratory epithelium. There were no tumors at any site distant from the respiratory epithelium. No other route of administration produced cancer at any site. These facts do not support the notion that acetaldehyde production may explain the proposed carcinogenicity of alcohol.

The induction of P4502E1 by ethanol and the consequent activation of nitrosamines to reactive intermediates is frequently cited as a possible mechanism of the co-carcinogenic action of alcohol. P4502E1 is an enzyme that metabolizes many small molecules. It is also induced and inhibited by a wide variety of compounds in food and during some physiologic states. This is a complicated interaction and it very well may have some application when considering the interaction with tobacco smoke, but it is totally inconsistent with the data simply to label "alcoholic beverages" independently as a "known carcinogen".

SLIDE 1

"--the effect of alcohol among lifelong nonsmokers has been clearly demonstrated (Baron et al., 1993; Blot et al., 1988; Ng et al., 1993)" **Longnecker and Tseng, in press; (Essentially same statement in Longnecker , 1995)**

-"had never used tobacco products on a daily basis for a period of at least 1 year" -----"The association of beer **(but not wine or liquor)** *and cancer of the oral cavity may have little to do with the alcohol content of beer. Contaminants ---- may be important etiologic factors."*
Ng et al., 1993

SLIDE 2

Blot et al., 1988: No dose response or significant increase in odds ratios with less than 30 drinks per week in nonsmokers (less than 100 cigarettes or cigars or pipes for no more than 6 months)

Baron et al., 1993: No nondrinker group (Italy); Control group <35 drinks per week; "heavy" (35-59 drinks per week) and "very heavy" (60 or more drinks per week) drinker but nonsmoker cases few (1-4) in each of 6 categories (confidence interval not calculated)

SLIDE 3

Case-control, oral-pharyngeal, with raw data on nonsmokers (others contain only adjusted data)

Bross and Coombs, 1976: No significant increase

Martinez, 1969: *Decrease* below 5 drinks per day

Elwood et al., 1984: *Decrease* below 17 drinks/week

Brugere et al., 1986: Nondrinkers: 40 gm/day (France)

Franceschi et al., 1990: Nondrinkers: 5 drinks/day (Italy)

Others not cited:

Day et al., 1993: No sig. increase below 30 drinks/week

Kabat et al., 1994: No sig. increase below 7 oz/day

Nam et al., 1992: *Decrease* below 24 drinks/week

SLIDE 4

Case-control, laryngeal, studies with raw data on nonsmokers (others contain only adjusted data)

Dosemeci et al., 1997: (Adjusted, but no dose response)

Wynder et al., 1956: Only *one* nonsmoker who drank

Wynder et al.,1976: *No* nonsmokers in drinker series

Elwood et al., 1984: (Extrinsic larynx combined with oral-pharyngeal; comments under oral-pharyngeal)

SLIDE 5

Case-control, esophageal, with raw data on nonsmokers (others contain only adjusted data)

De Stefani et al., 1990: (Adjusted, but no increase below 10 drinks/day)

Cheng et al., 1992: (Adjusted, but no sig. increase below 12 drinks/day)

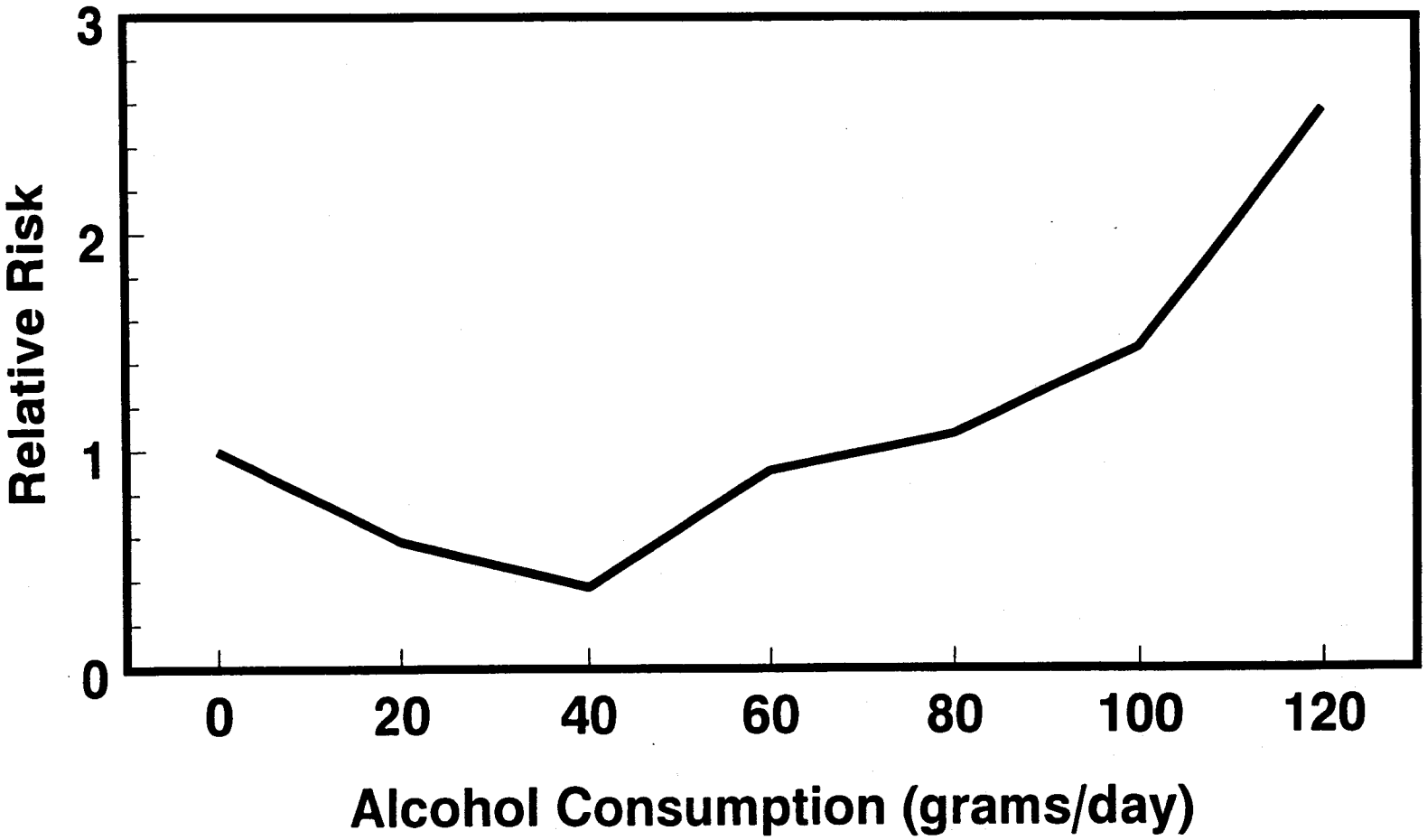
Gao et al.,1994: No sig. increase at any level of drinking

Others not cited:

Tuyns, 1983: Decrease below 60 gms/day "J" curve

SLIDE 6

Relative Risks of Esophageal Cancer Non-Smoking Drinkers (Tuyns 1983 data)



SLIDE 7

Mechanisms of Carcinogenesis Proposed in Document

1. **Acetaldehyde: Is only carcinogenic to animals by inhalation and at doses that cause necrosis of respiratory epithelium.**
2. **Induction of P4502E1 to increase production of proximal carcinogen from nitrosamines: Ethanol also *inhibits* P4502E1 (depending on dose and timing); fasting, obesity, unsaturated lipids, many common foods, thiamine deficiency also affect P4502E1 by induction and/or inhibition**